

Transient imine directing groups for C–H functionalisation

In chemistry, ‘organic’ molecules are defined as having a carbon-based structure and are found in all living systems. They can also be designed and synthesised for application in numerous industries, for example as pharmaceuticals, agrochemicals, cosmetics, paints, LCDs, dyes, and food additives. Each carbon atom requires four bonds to complete its valence and be stable; most frequently this is as bonds to hydrogen. Until recently, these carbon-hydrogen (C–H) bonds have been viewed as chemically inert, and reactions were conducted by manipulating bonds to other elements. However, C–H bonds are increasingly being used to do chemical reactions through “activation” of the C–H bond by a transition metal, forming a carbon-metal bond (C–H activation) and replacement of this new C–metal bond with a different group (C–H functionalisation). The challenge is how to select the desired C–H bond over all other C–H bonds on the organic molecule, which can be overcome by use of “directing groups”. Directing groups grab the metal, fixing it into position close to the targeted C–H bond, so that site-selective C–H activation can occur. However, directing groups are generally not wanted in the final compound, and so after C–H functionalisation they need to be removed. They also require installation onto the molecule prior to C–H functionalisation. These additional steps are inefficient and hinder the use of C–H functionalisation as a viable synthetic approach in industry.

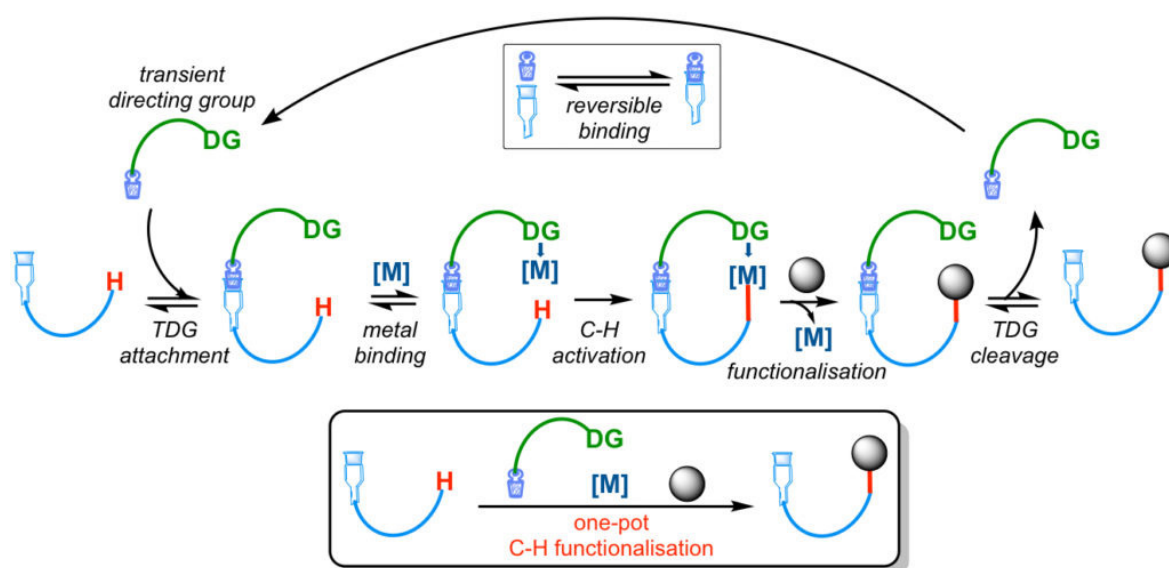


Fig. 1.

“Transient” directing groups offer a solution (Fig. 1). These are bound to the C–H functionalisation substrate *reversibly* so that directing group installation, C–H functionalisation and directing group cleavage occurs in one-pot. To achieve this, a reversible chemical bond is needed. Imines are readily formed (by condensation of aldehydes and amines) and cleaved under acidic conditions, and as such they have been exploited to form effective transient directing groups.

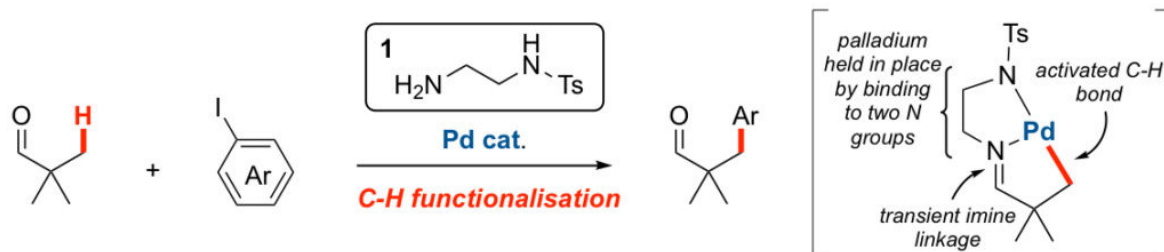


Fig. 2.

In our work, a simple amine, *N*-tosylethylenediamine (**1**, in Fig. 2) was shown to form a suitable transient imine directing group with aliphatic aldehydes. This facilitated a site selective one-pot palladium catalysed C–H arylation with aryl iodide coupling partners. Functionalisation occurred selectively on the β-C–H bond, leaving the aldehyde (generally considered as a highly reactive centre) intact. To understand the progress of the reaction, we isolated an important intermediate to demonstrate the formation of a carbon-palladium bond, as enabled by the directing group. By obtaining an X-ray crystal structure of this intermediate we were able to observe the types of interactions the directing group can make to position the catalyst appropriately to undertake the desired functionalisation.

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[Single operation palladium catalysed C\(sp³\)-H functionalisation of tertiary aldehydes: investigations into transient imine directing groups.](#)

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